



Editorial

Synergy, Antagonism, and Scientific Process

Make haste slowly.

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(1601-1658)

In the July 25 issue of the journal *Science*, John A. McLachlan of the Tulane-Xavier Center for Bioenvironmental Research, Tulane University, New Orleans, Louisiana, withdrew a previously published paper in which the authors had reported marked synergistic effects of several environmental chemicals on the activation of the estrogen receptor in a yeast reporter system (1). The possibility of synergistic interactions between weakly estrogenic chemicals found in the environment has very important mechanistic and public health implications.

In their *Science* paper McLachlan and colleagues reported that combinations of chemicals could activate the estrogen receptor to a degree several orders of magnitude above that produced by the individual chemicals (2). The biological effects of estrogen are mediated by high-affinity receptor proteins located in target cells. The consequences of estrogen receptor activation are far reaching because of its regulation of estrogen-responsive genes and because many industrial chemicals can interact with estrogen receptors, thereby disrupting normal endocrine functions. Disruption of normal endocrine functions through chemical interactions with the estrogen receptor could possibly be, in part, responsible for infertility, endometriosis, and cancers of the breast, uterus, and prostate.

Laboratories at Texas A&M University, Duke University, NIEHS, and the Chemical Industry Institute of Toxicology, tried to repeat the experiments of Arnold et al. (2), but without success. These laboratories expressed their concerns in a combined technical note published in the January 1997 issue of *Science* (3). This was followed by two other papers, which looked at several estrogen-receptor assays, and again synergism between weakly estrogenic chemicals was not detected (4,5). McLachlan and colleagues were unable to confirm their own data and, finally, their original *Science* paper was withdrawn. Withdrawal of their paper received the attention of major national newspapers and news services. Following the announcement of withdrawal, some inquiries have been made to this office regarding the standing of several recent articles published in *Environmental Health Perspectives* by the McLachlan group. These questions have ranged from expressions of environmental concern to direct statements regarding reliability of published data.

Three papers have been published in *Environmental Health Perspectives* by the McLachlan group that referenced their now-withdrawn *Science* paper. The first paper subsequent to the *Science* paper was a commentary that directly addressed synergistic interactions with estrogen receptors (6). The commentary reviewed and discussed the synergistic activation of the estrogen receptor by environmental chemicals, but considered the data presented in the *Science* article simply as confirmatory of synergistic action. The article was a commentary in which some degree of speculation is permissible and no new data were presented. Two other papers published in *Environmental Health Perspectives* by McLachlan and colleagues that simply referenced the withdrawn *Science* paper are not affected by the withdrawal (7,8), and EHP is confident that the data in those papers should be in the scientific literature as they represent important contributions to our understanding of chemical interactions with the estrogen receptor.

The history of science includes investigators who have clung to untenable positions maintaining their delusions to the bitter end, and

most withdrawals were forced only after evidence had been offered suggesting some form of misconduct. The voluntary withdrawal of a scientific paper because the data cannot be substantiated is a rare event. While these actions have been very painful for all involved, they are an essential part of the process that makes science a unique human enterprise. In science, the fallibility of human involvement is minimized over time by observing and reobserving, testing and retesting. Data that do not support the consensual reality of science are replaced or quickly forgotten. In facilitating this process by withdrawing their paper, McLachlan and his colleagues have served science appropriately and well.

These recent circumstances surrounding synergy in yeast have distracted us from the larger issues. We know from our experiences with PCBs and several pesticide formulations that synergy and antagonism may occur in circumstances of multiple chemical exposures. However, the scientific and regulatory communities have not developed credible strategies for designing mixture studies, *in vitro* or *in vivo*, to adequately address the issues of synergy, antagonism, or additivity. Moreover, we do not know how to best analyze the available data or how to package the information for use in risk assessment. These deficiencies must be addressed if we expect to properly evaluate health effects arising not only from environmental estrogens but chemical mixtures in general.

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